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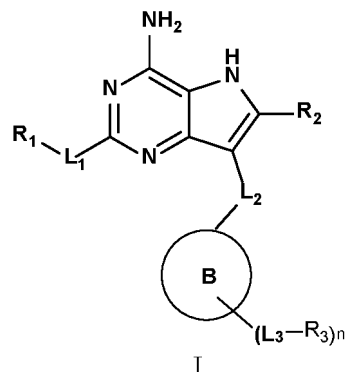
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(54) **DRUG COMBINATION CONTAINING TLR7 AGONIST**

(57) A drug combination containing a TLR7 agonist. Specifically, a drug combination jointly using the compound of formula I acting as a TLR7 agonist and entecavir for the treatment of hepatitis B virus infection and a use thereof, the drug combination having a good anti-hepatitis B virus infection effect.



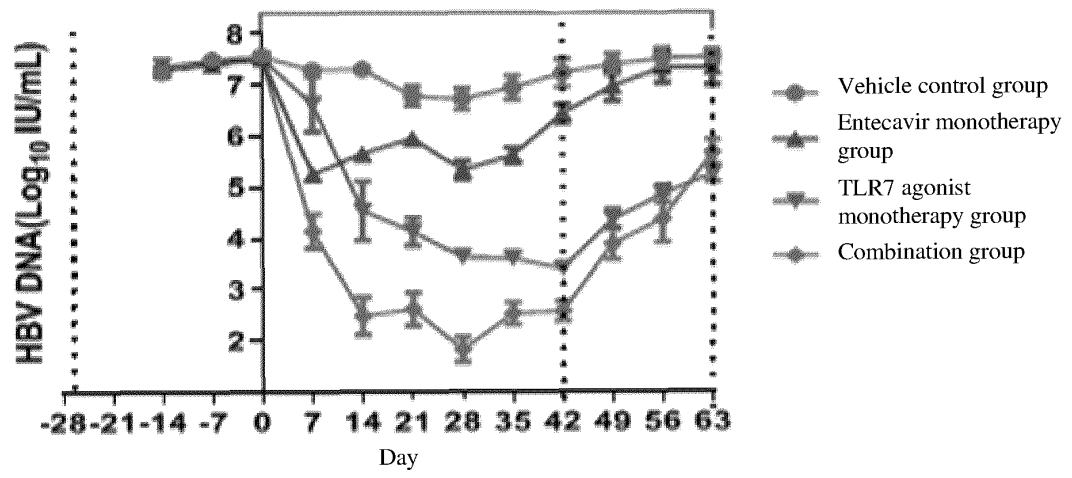


FIG. 1

Description**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] The present application claims benefit and priority to the Chinese Patent No. 201910933558.8 filed with the National Intellectual Property Administration, PRC on September 29, 2019, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present application relates to the field of medicinal chemistry, particularly, to a pharmaceutical combination comprising a TLR7 agonist, and more particularly, to a pharmaceutical combination of a compound of formula I as a TLR7 agonist and entecavir for combined use in treating hepatitis B virus infection and use thereof.

BACKGROUND

[0003] As summarized by the World Health Organization, about 257 million people worldwide are infected with hepatitis B virus (HBV). If not well treated, patients with hepatitis will be confronted with long-term fatal diseases such as liver failure, cirrhosis and liver cancer.

[0004] Conventional drugs currently approved for the treatment of chronic hepatitis B include nucleosides (nucleotides) and interferons. Nucleosides (nucleotides), such as entecavir, can inhibit HBV DNA replication.

[0005] Toll-like receptors are expressed in a variety of immune cells. Toll-like receptors recognize highly conserved structural motifs: pathogen-associated molecular patterns (PAMPs) expressed by microbial pathogens or damage-associated molecular patterns (DAMPs) released by necrotic cells. Toll-like receptors are stimulated by corresponding PAMPs or DAMPs to induce signaling cascade, leading to activation of transcription factors such as AP-1, NF- κ B and interferon regulatory factors (impulse response function). As such, a variety of cellular reactions are induced, including production of interferons, proinflammatory cytokines and effector cytokines, thus promoting immune response. 13 toll-like receptors have been found in mammals so far. Toll-like receptors 1, 2, 4, 5 and 6 are mainly expressed on the cell surface while toll-like receptors 3, 7, 8 and 9 are expressed in endosomes. Different toll-like receptors recognize ligands derived from different pathogens. Toll-like receptor 7 (TLR7) is mainly expressed by plasmacytoid dendritic cells (pDCs) and induces secretion of the interferon alpha (IFN- α) by ligand recognition. Some TLR7 agonists have been reported, for example, imiquimod, resiquimod and GS-9620. WO2016023511 and WO2017076346, which are incorporated herein by reference in their entireties, disclose a class of novel TLR7 agonists demonstrating good bioactivity and selectivity.

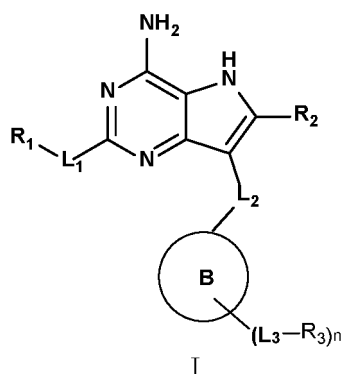
[0006] Although patients with hepatitis B virus infection have many treatment options, there is still a need for more potent therapeutic agents for clinical use.

SUMMARY OF THE INVENTION

[0007] In one aspect, the present application provides a pharmaceutical combination, comprising a compound of formula I or a pharmaceutically acceptable salt thereof and entecavir or a pharmaceutically acceptable salt or solvate thereof.

[0008] In another aspect, the present application further provides use of the pharmaceutical combination disclosed herein for the manufacture of a medicament for treating hepatitis B virus infection. The present application further provides a method for treating hepatitis B virus infection, comprising administering to a subject in need thereof an effective amount of the pharmaceutical combination disclosed herein. The present application further provides the pharmaceutical combination for use in the treatment of hepatitis B virus infection. The present application further provides use of the pharmaceutical combination disclosed herein for treating hepatitis B virus infection.

[0009] In one aspect, the present application provides a pharmaceutical combination, comprising a compound of formula I or a pharmaceutically acceptable salt thereof and entecavir or a pharmaceutically acceptable salt or solvate thereof, the compound of formula I is shown as follows:



wherein,

L_1 is selected from -O-;

L_2 is selected from -CH₂-, wherein the -CH₂- is optionally substituted with R_4 ;

R_1 is selected from the group consisting of hydrogen and C₁₋₁₀ alkyl, wherein the C₁₋₁₀ alkyl is optionally substituted with R_5 ;

R_2 is selected from the group consisting of hydrogen, cyano, -COOH and -CONH₂, wherein the -COOH and -CONH₂ are optionally substituted with R_6 ;

B is selected from the group consisting of 6-10 membered aryl and 5-10 membered heteroaryl;

L_3 is selected from the group consisting of C₀₋₆ alkylene and imino, wherein the C₀₋₆ alkylene and imino are optionally substituted with R_7 ;

R_3 is selected from the group consisting of hydrogen, amino, C₁₋₁₀ alkyl, C₃₋₁₀ cyclohydrocarbyl, 3-10 membered heterocyclohydrocarbyl, 6-10 membered aryl and 5-10 membered heteroaryl, wherein the amino, C₁₋₁₀ alkyl, C₃₋₁₀ cyclohydrocarbyl, 3-10 membered heterocyclohydrocarbyl, 6-10 membered aryl and 5-10 membered heteroaryl are optionally substituted with R_8 , or

R_3 and L_3 , together with an ortho atom on ring B, form a saturated or unsaturated 5-8 membered ring, wherein the 5-8 membered ring is optionally substituted with R_9 ;

n is 0, 1, 2, 3, 4 or 5;

R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are each independently selected from halogen, cyano, hydroxy, sulfydryl, amino, -R, -OR, =O, -SR, -NHR and -NR₂; R is independently selected from C₁₋₈ alkyl, C₃₋₈ cyclohydrocarbyl, 3-8 membered heterocyclohydrocarbyl, 6-8 membered aryl and 5-8 membered heteroaryl.

[0010] In some embodiments of the compound of formula I, L_2 is selected from -CH₂-.

[0011] In some embodiments of the compound of formula I, R_1 is selected from C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with one or more R_5 .

[0012] In some embodiments of the compound of formula I, R_2 is selected from the group consisting of hydrogen, cyano and -CONH₂, wherein the -CONH₂ is optionally substituted with one or more R_6 .

[0013] In some embodiments of the compound of formula I, B is selected from the group consisting of 6-7 membered aryl and 5-7 membered heteroaryl. In some embodiments of the compound of formula I, B is selected from the group consisting of phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thienyl, thiazolyl, furanyl, oxazolyl, thiadiazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl and triazolyl. In some embodiments of the compound of formula I, B is selected from the group consisting of phenyl, pyridinyl and thiazolyl.

[0014] In some embodiments of the compound of formula I, L_3 is selected from C₀₋₆ alkylene, wherein the C₀₋₆ alkylene is optionally substituted with one or more R_7 .

[0015] In some embodiments of the compound of formula I, R_3 is selected from the group consisting of hydrogen,

amino, C₁₋₆ alkyl, C₃₋₈ cyclohydrocarbyl, 3-8 membered heterocyclohydrocarbyl, 6-8 membered aryl and 5-8 membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₃₋₈ cyclohydrocarbyl, 3-8 membered heterocyclohydrocarbyl, 6-8 membered aryl and 5-8 membered heteroaryl are optionally substituted with one or more R₈; or R₃ and L₃, together with an ortho atom on ring B, form a saturated or unsaturated 5-8 membered ring, wherein the 5-8 membered ring is optionally substituted with one or more R₉. In some embodiments of the compound of formula I, R₃ is selected from the group consisting of hydrogen, amino, C₁₋₆ alkyl, piperazinyl, morpholinyl, tetrahydropyrrolyl, piperidinyl, azetidiny, diazepanyl and 2-oxa-5-azabicyclo[2.2.1]heptyl, wherein the amino, C₁₋₆ alkyl, piperazinyl, morpholinyl, tetrahydropyrrolyl, piperidinyl, azetidiny, diazepanyl and 2-oxa-5-azabicyclo[2.2.1]heptyl are optionally substituted with one or more R₈; or R₃ and L₃, together with an ortho atom on ring B, form a saturated or unsaturated 6 membered ring, wherein the 6 membered ring is optionally substituted with one or more R₉.

[0016] In some embodiments of the compound of formula I, R₄, R₅, R₆, R₇, R₈ and R₉ are each independently selected from the group consisting of halogen, -R, -OR and =O.

[0017] In some embodiments of the present application, the compound of formula I or the pharmaceutically acceptable salt thereof is selected from the group consisting of:

2-butoxy-7-(3-((4-methylpiperazin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(3-(morpholinomethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

7-(3-(aminomethyl)benzyl)-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(3-(pyrrolidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-((3,3-difluoropyrrolidin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-((3-fluoropyrrolidin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

1-(4-((4-amino-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)benzyl)pyrrolidin-3-ol;

2-butoxy-7-(4-(piperidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-(morpholinomethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-((4-methylpiperazin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-((dimethylamino)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-((diethylamino)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-((dipropylamino)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

7-(4-(azetidin-1-ylmethyl)benzyl)-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-((3-methoxylazetidin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-(4-methyl-1,4-diazepan-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-((2,6-dimethylmorpholino)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

7-(4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-ylmethyl)benzyl)-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-((4-methoxypiperidin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-((4-isopropylpiperazin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(6-(pyrrolidin-1-ylmethyl)pyridin-3-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(3-(2-(pyrrolidin-1-yl)ethyl)benzyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 2-butoxy-7-(4-(1-(pyrrolidin-1-yl)ethyl)benzyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 5 2-butoxy-7-(4-(1-methylpiperidin-4-yl)benzyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 2-butoxy-7-(4-(1-methylpyrrolidin-2-yl)benzyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 10 1-(4-((4-amino-2-butoxy-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methyl)phenyl)-4-methylpiperazin-2-one;
 7-benzyl-2-(2-methoxyethoxy)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 2-(2-methoxyethoxy)-7-((6-methylpyridin-3-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 15 7-((5-chloropyridin-2-yl)methyl)-2-(2-methoxyethoxy)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 2-(2-methoxyethoxy)-7-((6-(pyrrolidin-1-ylmethyl)pyridin-3-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 1-(4-((4-amino-2-(2-methoxyethoxy)-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)methyl)phenyl)-4-methylpiperazin-2-one;
 20 2-butoxy-7-((5-(pyrrolidin-1-ylmethyl)pyridin-2-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 4-amino-2-butoxy-7-((6-(pyrrolidin-1-ylmethyl)pyridin-3-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-6-carbonitrile;
 25 4-amino-2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-6-carbonitrile;
 4-amino-2-butoxy-7-(4-(morpholinomethyl)benzyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-6-carbonitrile;
 4-amino-2-butoxy-7-(4-((4-methylpiperazin-1-yl)methyl)benzyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-6-carbonitrile;
 30 4-amino-2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-6-carboxamide;
 2-butoxy-7-((1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 35 2-butoxy-7-((2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 2-butoxy-7-((2-ethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 2-butoxy-7-((2-isopropyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 40 2-butoxy-7-((1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 2-butoxy-7-((2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine;
 45 2-butoxy-7-((2-ethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine; and
 2-butoxy-7-((2-(pyrrolidin-1-ylmethyl)thiazol-5-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine, or a pharmaceutically acceptable salt thereof.

50 **[0018]** In some embodiments of the present application, the compound of formula I or the pharmaceutically acceptable salt thereof is selected from the group consisting of 2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine or a pharmaceutically acceptable salt thereof, and 2-butoxy-7-((2-(pyrrolidin-1-ylmethyl)thiazol-5-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine or a pharmaceutically acceptable salt thereof.

55 **[0019]** In some embodiments of the present application, the entecavir solvate is selected from an entecavir hydrate. In some embodiments, the entecavir hydrate is selected from the group consisting of entecavir 0.5-2 hydrate. The entecavir hydrate is selected from entecavir monohydrate.

[0020] In some embodiments of the present application, the pharmaceutically acceptable salt of entecavir is selected from a maleate salt. In some embodiments of the present application, the pharmaceutically acceptable salt of entecavir

is selected from a monomaleate salt.

[0021] In some embodiments of the present application, entecavir or the pharmaceutically acceptable salt or solvate thereof is selected from the group consisting of entecavir monomaleate, entecavir monohydrate and entecavir monomaleate monohydrate.

[0022] In some embodiments of the present application, the pharmaceutical combination comprises 2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine or a pharmaceutically acceptable salt thereof, and entecavir or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical combination disclosed herein comprises 2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine or a maleate or trifluoroacetate salt thereof, and entecavir or a pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the pharmaceutical combination disclosed herein comprises 2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine and entecavir or a monohydrate thereof.

[0023] In some embodiments of the present application, the pharmaceutical combination comprises 2-butoxy-7-((2-(pyrrolidin-1-ylmethyl)thiazol-5-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine or a pharmaceutically acceptable salt thereof, and entecavir or a solvate thereof. In some embodiments, the pharmaceutical combination disclosed herein comprises 2-butoxy-7-((2-(pyrrolidin-1-ylmethyl)thiazol-5-yl)methyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine and entecavir monomaleate monohydrate.

[0024] In some embodiments of the present application, the compound of formula I or the pharmaceutically acceptable salt thereof in the pharmaceutical combination can be administered once every day, twice every day, once every two days, once every three days, once every four days, or once every five days, at a dose of 0.0001 to 20 mg/kg body weight (on the basis of the weight of the compound of formula I).

[0025] In some embodiments of the present application, entecavir or the pharmaceutically acceptable salt or solvate thereof in the pharmaceutical combination can be administered once every day, twice every day, or once every two days, at a dose of 0.5 mg or 1.0 mg (on the basis of the weight of entecavir).

[0026] In some embodiments of the present application, an average daily dose of entecavir or the pharmaceutically acceptable salt or solvate thereof in the pharmaceutical combination is 0.005 mg to 10.0 mg. In some embodiments of the present application, the average daily dose of entecavir or the pharmaceutically acceptable salt or solvate thereof in the pharmaceutical combination is 0.05 mg to 5.0 mg. In some embodiments of the present application, the average daily dose of entecavir or the pharmaceutically acceptable salt or solvate thereof in the pharmaceutical combination is 0.10 mg to 2.0 mg. In some embodiments of the present application, the average daily dose of entecavir or the pharmaceutically acceptable salt or solvate thereof in the pharmaceutical combination is 0.25 mg to 2.0 mg. In some embodiments of the present application, the average daily dose of entecavir or the pharmaceutically acceptable salt or solvate thereof in the pharmaceutical combination is 0.5 mg to 1.0 mg.

[0027] In some embodiments of the present application, an average daily dose ratio (on weight basis) of the compound of formula I or the pharmaceutically acceptable salt thereof to entecavir or the pharmaceutically acceptable salt or solvate thereof in the pharmaceutical combination is selected from 10:1 to 1:10. In some embodiments, the average daily dose ratio (on weight basis) of the compound of formula I or the pharmaceutically acceptable salt thereof to entecavir or the pharmaceutically acceptable salt or solvate thereof is selected from the group consisting of 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.7, 1:1.8, 1:1.9, 1:2, 1:2.1, 1:2.2, 1:2.3, 1:2.4, 1:2.5, 1:2.6, 1:2.7, 1:2.8, 1:2.9, 1:3, 1:3.1, 1:3.2, 1:3.3, 1:3.4, 1:3.5, 1:3.6, 1:3.7, 1:3.8, 1:3.9, 1:4, 1:4.1, 1:4.2, 1:4.3, 1:4.4, 1:4.5, 1:4.6, 1:4.7, 1:4.8, 1:4.9, 1:5, 1:5.1, 1:5.2, 1:5.3, 1:5.4, 1:5.5, 1:5.6, 1:5.7, 1:5.8, 1:5.9, 1:6, 1:6.1, 1:6.2, 1:6.3, 1:6.4, 1:6.5, 1:6.6, 1:6.7, 1:6.8, 1:6.9, 1:7, 1:7.1, 1:7.2, 1:7.3, 1:7.4, 1:7.5, 1:7.6, 1:7.7, 1:7.8, 1:7.9, 1:8, 1:8.1, 1:8.2, 1:8.3, 1:8.4, 1:8.5, 1:8.6, 1:8.7, 1:8.8, 1:8.9, 1:9, 1:9.1, 1:9.2, 1:9.3, 1:9.4, 1:9.5, 1:9.6, 1:9.7, 1:9.8, 1:9.9, 1:10, and a range formed by any of the ratios. In some embodiments, the average daily dose ratio (on weight basis) of the compound of formula I or the pharmaceutically acceptable salt thereof to entecavir or the pharmaceutically acceptable salt or solvate thereof is preferably selected from the group consisting of 1:1.5 to 1:4, 1:1.6 to 1:3.8, 1:1.8 to 1:3.8, 1:1.8 to 1:3.6 and 1:2 to 1:3.5.

[0028] In some embodiments of the present application, the pharmaceutical combination is a fixed combination. In some embodiments, the fixed combination is in the form of a solid pharmaceutical composition. In some embodiments, the compound of formula I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof in the fixed combination are present in the same solid pharmaceutical composition.

[0029] In some embodiments of the present application, the pharmaceutical combination is a non-fixed combination. In some embodiments, the compound of formula I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof in the non-fixed combination are each in the form of a solid pharmaceutical composition. In some embodiments, the compound of formula I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof in the non-fixed combination are each in the form of a solid pharmaceutical composition, and the solid pharmaceutical composition of the compound of formula I or the pharmaceutically acceptable salt thereof and the solid pharmaceutical composition of entecavir or the pharmaceutically acceptable salt or solvate thereof are present in the same sachet. In some embodiments, the compound of formula

I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof in the non-fixed combination are each in the form of a solid pharmaceutical composition, and the solid pharmaceutical composition of the compound of formula I or the pharmaceutically acceptable salt thereof and the solid pharmaceutical composition of entecavir or the pharmaceutically acceptable salt or solvate thereof are not present in the same sachet.

[0030] In some embodiments of the present application, the solid pharmaceutical composition is selected from the group consisting of a tablet and a capsule.

[0031] In another aspect, the present application further provides use of the pharmaceutical combination disclosed herein for the manufacture of a medicament for treating hepatitis B virus infection. The pharmaceutical combination is as described above.

[0032] In another aspect, the present application further provides a method for treating hepatitis B virus infection, comprising administering to a subject in need thereof an effective amount of the pharmaceutical combination disclosed herein. The pharmaceutical combination is as described above.

[0033] In another aspect, the present application further provides the pharmaceutical combination disclosed herein for use in the treatment of hepatitis B virus infection. The pharmaceutical combination is as described above.

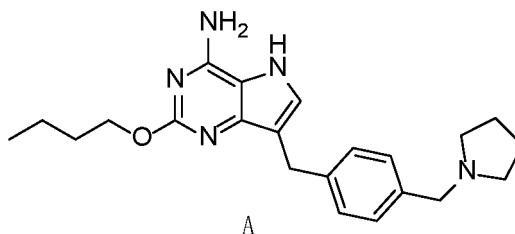
[0034] In another aspect, the present application further provides use of the pharmaceutical combination disclosed herein for treating hepatitis B virus infection. The pharmaceutical combination is as described above.

[0035] In some embodiments of the present application, the present application provides use of the compound of formula I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof in preparing a medicament for treating hepatitis B virus infection, wherein the compound of formula I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof are separately prepared into pharmaceutical compositions.

[0036] In some embodiments of the present application, the present application further provides a kit for treating hepatitis B virus infection, comprising: (a) a first pharmaceutical composition comprising the compound of formula I or the pharmaceutically acceptable salt thereof as active ingredient; (b) a second pharmaceutical composition comprising entecavir or the solvate thereof as active ingredient; and optionally, (c) a package insert for combined use of the compound of formula I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof.

Compound of formula I or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof

[0037] In some embodiments, the compound of formula I or the pharmaceutically acceptable salt thereof is selected from a compound of formula A or a pharmaceutically acceptable salt thereof:



[0038] The compound of formula A is known in the prior art and has the chemical name 2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine, of which the preparation and chemical properties are described in WO2016023511.

[0039] In some embodiments, the pharmaceutically acceptable salt of the compound of formula A is selected from the group consisting of a maleate salt or a fumarate salt.

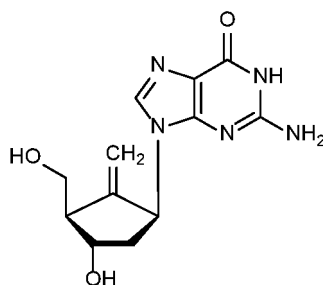
[0040] In some embodiments, the pharmaceutical composition of the compound of formula A or the pharmaceutically acceptable salt thereof is selected from a solid pharmaceutical composition, preferably selected from the group consisting of a tablet and a capsule.

[0041] In some embodiments, the compound of formula A or the pharmaceutically acceptable salt thereof is in the form of a pharmaceutical composition having a unit dose of 0.01 mg to 10 mg, preferably a pharmaceutical composition having a unit dose of 0.01 mg, 0.02 mg, 0.05 mg, 0.08 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2.0 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6 mg, 2.7 mg, 2.8 mg, 2.9 mg, 3.0 mg, 3.1 mg, 3.2 mg, 3.3 mg, 3.4 mg, 3.5 mg, 3.6 mg, 3.7 mg, 3.8 mg, 3.9 mg, 4.0 mg, 4.1 mg, 4.2 mg, 4.3 mg, 4.4 mg, 4.5 mg, 4.6 mg, 4.7 mg, 4.8 mg, 4.9 mg, 5.0 mg, 5.1 mg, 5.2 mg, 5.3 mg, 5.4 mg, 5.5 mg, 5.6 mg, 5.7 mg, 5.8 mg, 5.9 mg, 6.0 mg, 6.1 mg, 6.2 mg, 6.3 mg, 6.4 mg, 6.5 mg, 6.6

mg, 6.7 mg, 6.8 mg, 6.9 mg, 7.0 mg, 7.1 mg, 7.2 mg, 7.3 mg, 7.4 mg, 7.5 mg, 7.6 mg, 7.7 mg, 7.8 mg, 7.9 mg, 8.0 mg, 8.1 mg, 8.2 mg, 8.3 mg, 8.4 mg, 8.5 mg, 8.6 mg, 8.7 mg, 8.8 mg, 8.9 mg, 9.0 mg, 9.1 mg, 9.2 mg, 9.3 mg, 9.4 mg, 9.5 mg, 9.6 mg, 9.7 mg, 9.8 mg, 9.9 mg, 10.0 mg, or a range formed by any of the values.

Entecavir or pharmaceutically acceptable salt or solvate thereof, or pharmaceutical composition thereof

[0042] As used herein, entecavir has the chemical name 2-amino-9-[(1*S*,3*R*,4*S*)-4-hydroxy-3-hydroxymethyl-2-methylenecyclopentyl]-1,9-dihydro-6*H*-purin-6-one and the following structural formula:



[0043] In some embodiments, entecavir comprises a pharmaceutically acceptable salt thereof selected from a maleate salt. In some embodiments, the pharmaceutically acceptable salt of entecavir is selected from a monomaleate salt. In some embodiments, entecavir comprises a solvate thereof selected from an entecavir hydrate. In some embodiments, the entecavir hydrate is selected from the group consisting of entecavir 0.5-2 hydrate. In some embodiments, the entecavir hydrate is selected from entecavir monohydrate.

[0044] In some embodiments, entecavir is selected from the group consisting of entecavir monomaleate, entecavir monohydrate and entecavir monomaleate monohydrate.

[0045] In some embodiments, entecavir or the pharmaceutically acceptable salt or solvate thereof is in the form of a pharmaceutical composition. Preferably, the pharmaceutical composition is selected from a solid pharmaceutical composition. The solid pharmaceutical composition is preferably selected from the group consisting of a tablet and a capsule.

[0046] In some embodiments, the pharmaceutical composition of entecavir or the pharmaceutically acceptable salt or solvate thereof is selected from a pharmaceutical composition having a unit dose of 0.01 mg to 5 mg, preferably selected from a pharmaceutical composition having a unit dose of 0.01 mg, 0.02 mg, 0.05 mg, 0.08 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2.0 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6 mg, 2.7 mg, 2.8 mg, 2.9 mg, 3.0 mg, 3.1 mg, 3.2 mg, 3.3 mg, 3.4 mg, 3.5 mg, 3.6 mg, 3.7 mg, 3.8 mg, 3.9 mg, 4.0 mg, 4.1 mg, 4.2 mg, 4.3 mg, 4.4 mg, 4.5 mg, 4.6 mg, 4.7 mg, 4.8 mg, 4.9 mg, 5.0 mg, or a range formed by any of the values.

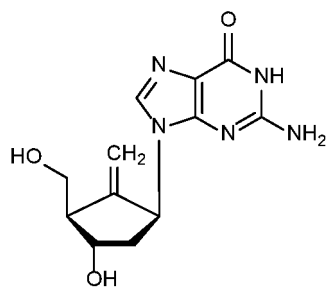
[0047] As used herein, entecavir or the pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition thereof may be selected from a commercially available product.

Definitions and Description

[0048] Unless otherwise stated, the following terms used herein shall have the following meanings. A certain term, unless otherwise specifically defined, should not be considered uncertain or unclear, but construed according to its common meaning in the field.

[0049] As used herein, the compound of formula I or the pharmaceutically acceptable salt thereof is a TLR7 agonist.

[0050] As used herein, entecavir has the chemical name 2-amino-9-[(1*S*,3*R*,4*S*)-4-hydroxy-3-hydroxymethyl-2-methylenecyclopentyl]-1,9-dihydro-6*H*-purin-6-one and the following structural formula:



[0051] As used herein, structural formulas and chemical names of a portion of the compounds of formula I or the pharmaceutically acceptable salts thereof are as follows:

Name/ Number	Structural formula	Chemical name
1		2-butoxy-7-((4-methylpiperazin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
2		2-butoxy-7-(3-(morpholinomethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
3		7-(3-(aminomethyl)benzyl)-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-4-amine
4		2-butoxy-7-(3-(pyrrolidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
5		2-butoxy-7-(4-((3,3-difluoropyrrolidin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
6		2-butoxy-7-(4-((3-fluoropyrrolidin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine

(continued)

Name/ Number	Structural formula	Chemical name
7		1-(4-((4-amino-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)benzyl)pyrrolidin-3-ol
8		2-butoxy-7-(4-(piperidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
9		2-butoxy-7-(4-(morpholinomethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
10		2-butoxy-7-(4-((4-methylpiperazin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
11		2-butoxy-7-(4-((dimethylamino)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
12		2-butoxy-7-(4-((diethylamino)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
13		2-butoxy-7-(4-((dipropylamino)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
14		7-(4-(azetidin-1-ylmethyl)benzyl)-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-4-amine

(continued)

Name/ Number	Structural formula	Chemical name
15		2-butoxy-7-(4-((3-methoxylazetidin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
16		2-butoxy-7-(4-((4-methyl-1,4-diazepan-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
17		2-butoxy-7-(4-((2,6-dimethylmorpholino)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
18		7-(4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-ylmethyl)benzyl)-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-4-amine
19		2-butoxy-7-(4-((4-methoxypiperidin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
20		2-butoxy-7-(4-((4-isopropylpiperazin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
21		2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine

(continued)

Name/ Number	Structural formula	Chemical name
22		2-butoxy-7-((6-(pyrrolidin-1-ylmethyl)pyridin-3-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
23		2-butoxy-7-(3-(2-(pyrrolidin-1-yl)ethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
24		2-butoxy-7-(4-(1-(pyrrolidin-1-yl)ethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
25		2-butoxy-7-(4-(1-methylpiperidin-4-yl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
26		2-butoxy-7-(4-(1-methylpyrrolidin-2-yl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
27		1-(4-((4-amino-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)phenyl)-4-methylpiperazin-2-one
28		7-benzyl-2-(2-methoxyethoxy)-5H-pyrrolo[3,2-d]pyrimidin-4-amine

(continued)

Name/ Number	Structural formula	Chemical name
29		2-(2-methoxyethoxy)-7-((6-methylpyridin-3-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
30		7-((5-chloropyridin-2-yl)methyl)-2-(2-methoxyethoxy)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
31		2-(2-methoxyethoxy)-7-((6-(pyrrolidin-1-ylmethyl)pyridin-3-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
32		1-(4-((4-amino-2-(2-methoxyethoxy)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)phenyl)-4-methylpiperazin-2-one
33		2-butoxy-7-((5-(pyrrolidin-1-ylmethyl)pyridin-2-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
34		4-amino-2-butoxy-7-((6-(pyrrolidin-1-ylmethyl)pyridin-3-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-6-carbonitrile
35		4-amino-2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-6-carbonitrile

(continued)

Name/ Number	Structural formula	Chemical name
36		4-amino-2-butoxy-7-(4-(morpholinomethyl)benzyl)- 5 <i>H</i> -pyrrolo [3 ,2- <i>d</i>]pyrimidin-6-carbonitrile
37		4-amino-2-butoxy-7-(4-((4-methylpiperazin-1-yl) methyl) benzyl)-5 <i>H</i> -pyrrolo[3,2- <i>d</i>]pyrimidin-6- carbonitrile
38		4-amino-2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)- 5 <i>H</i> -pyrrolo[3,2- <i>d</i>]pyrimidin-6-carboxamide
39		2-butoxy-7-((1,2,3,4-tetrahydroisoquinolin-7-yl) methyl)-5 <i>H</i> -pyrrolo[3 ,2- <i>d</i>]pyrimidin-4-amine
40		2-butoxy-7-((2-methyl-1,2,3,4-tetrahydroisoquinolin- 7-yl)methyl)-5 <i>H</i> -pyrrolo[3,2- <i>d</i>]pyrimidin-4-amine
41		2-butoxy-7-((2-ethyl-1,2,3,4-tetrahydroisoquinolin-7- yl) methyl)-5 <i>H</i> -pyrrolo[3,2- <i>d</i>]pyrimidin-4-amine
42		2-butoxy-7-((2-isopropyl-1,2,3,4- tetrahydroisoquinolin-7 -yl)methyl)-5 <i>H</i> -pyrrolo[3,2- <i>d</i>] pyrimidin-4-amine

(continued)

Name/ Number	Structural formula	Chemical name
43		2-butoxy-7-((1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
44		2-butoxy-7-((2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
45		2-butoxy-7-((2-ethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine
46		2-butoxy-7-((2-(pyrrolidin-1-ylmethyl)thiazol-5-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine

[0052] As used herein, the compound of formula I includes non-salt forms thereof (for example, free acids or free bases) and further includes pharmaceutically acceptable salts thereof. The non-salts or salts fall within the scope of protection of the present application. For example, the pharmaceutically acceptable salt of the compound of formula I may be a hydrochloride salt, a maleate salt or a fumarate salt.

[0053] As used herein, entecavir includes non-solvate forms thereof and further includes solvate forms thereof. The non-solvates or solvates fall within the scope of protection of the present application. When selected from solvate forms, the molar ratio of the compound to the solvent may be selected from the group consisting of 1:0.5, 1:1, 1:1.5, 1:2, or a range formed by any of the ratios, e.g., 1:0.5 to 1:2, 1:0.5 to 1:1.5, or 1:1 to 1:1.5. For example, entecavir is in the form of a non-solvate. For example, entecavir is in the form of a hydrate. For example, entecavir is in the form of a monohydrate.

[0054] As used herein, the dose is based on the weight of the free form of the compound, the free form of the compound referring to the non-salt and non-solvate form of the compound.

[0055] The term "substitute" or "substituted" means that any one or more hydrogen atoms on a specific atom are substituted with substituents, as long as the valence of the specific atom is normal and the resulting compound is stable. When the substituent is oxo (namely =O), it means that two hydrogen atoms are substituted, and oxo is not available on an aromatic group.

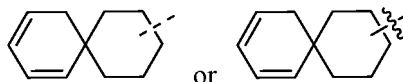
[0056] The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur. The description includes instances where the event or circumstance occurs and instances where the event or circumstance does not occur. For example, an ethyl optionally substituted with halogen, means that the ethyl may be unsubstituted (CH₂CH₃), monosubstituted (for example, CH₂CH₂F), polysubstituted (for example, CHFCH₂F, CH₂CHF₂ and the like) or fully substituted (CF₂CF₃). It will be understood by those skilled in the art that for any groups comprising one or more substituents, any substitutions or substituting patterns which may not exist spatially or cannot be synthesized are not introduced.

[0057] C_{m-n} used herein means that the portion has an integer number of carbon atoms in the given range. For example, "C₁₋₆" means that the group may have 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms.

[0058] When any variable (e.g., R) occurs more than once in the constitution or structure of a compound, the variable is independently defined in each case. Therefore, for example, if a group is substituted with 2 Rs, the R has independent option at each case.

[0059] When the number of a linking group is 0, for example, $-(CH_2)_0-$, it means that the linking group is a covalent bond.

[0060] When a bond of a substituent is cross-linked to two atoms on a ring, the substituent can be bonded to any atom on the ring. For example, structural unit



represents that substitution may occur at any one position of cyclohexyl or cyclohexadienyl.

[0061] The term "halo-" or "halogen" refers to fluorine, chlorine, bromine and iodine.

[0062] The term "hydroxyl" refers to -OH group.

[0063] The term "cyano" refers to -CN group.

[0064] The term "sulfydryl" refers to -SH group.

[0065] The term "amino" refers to -NH₂ group.

[0066] The term "alkyl" refers to hydrocarbyl with a general formula of C_nH_{2n+1}. The alkyl can be linear or branched. For example, the term "C₁₋₆ alkyl" refers to alkyl with 1-6 carbon atoms (for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, *tert*-butyl, *n*-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, hexyl, 2-methylpentyl, etc.). Similarly, the alkyl portions (namely alkyl) of alkoxy, monoalkylamine, dialkylamine, alkylsulfonyl and alkylsulfanyl have the same meaning as defined above.

[0067] The term "alkoxy" refers to -O-alkyl.

[0068] The term "cycloalkyl" refers to a carbon ring that is fully saturated and may exist as a monocyclic, bridged cyclic or spiro cyclic structure. Unless otherwise specified, the carbon ring is generally a 3-10 membered ring. Non-limiting examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl (bicyclo[2.2.1]heptyl), bicyclo[2.2.2]octyl, adamantyl, and the like.

[0069] The term "cyclohydrocarbyl" refers to a saturated or unsaturated nonaromatic cyclic hydrocarbyl consisting of carbon atoms and hydrogen atoms, preferably containing 1 or 2 rings. The cyclohydrocarbyl can be of a monocyclic, fused polycyclic, bridged cyclic or spiro cyclic structure. Non-limiting examples of cyclohydrocarbyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl, spiro[3.3]heptyl, and the like.

[0070] The term "heterocyclyl" refers to a fully saturated or partially unsaturated (but not fully unsaturated heteroaromatic group) nonaromatic ring which may exist in the form of a monocyclic, bridged cyclic or spiro cyclic structure. Unless otherwise specified, the heterocyclyl is usually a 3-7 membered ring containing 1-3 heteroatoms (preferably 1 or 2 heteroatoms) independently selected from the group consisting of sulfur, oxygen and/or nitrogen. Non-limiting examples of heterocyclyl include, but are not limited to, oxiranyl, tetrahydrofuranyl, dihydrofuranyl, pyrrolidinyl, *N*-methylpyrrolidinyl, dihydropyrrolyl, piperidinyl, piperazinyl, pyrazolidinyl, 4*H*-pyranyl, morpholinyl, thiomorpholinyl, tetrahydrothienyl and the like.

[0071] The term "heterocycloalkyl" refers to a fully saturated cyclic group that may exist in the form of a monocyclic, bridged cyclic or spiro cyclic structure. Unless otherwise specified, the heterocyclyl is usually a 3-7 membered ring containing 1-3 heteroatoms (preferably 1 or 2 heteroatoms) independently selected from the group consisting of sulfur, oxygen and/or nitrogen. Examples of 3 membered heterocycloalkyl include, but are not limited to, oxiranyl, thiiranyl, and aziranyl; non-limiting examples of 4 membered heterocycloalkyl include, but are not limited to, azetidiny, oxetanyl, and thietanyl; examples of 5 membered heterocycloalkyl include, but are not limited to, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, isoxazolidinyl, oxazolidinyl, isothiazolidinyl, thiazolidinyl, imidazolidinyl, and tetrahydropyrazolyl; examples of 6 membered heterocycloalkyl include, but are not limited to, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, piperazinyl, 1,4-thioxanyl, 1,4-dioxanyl, thiomorpholinyl, 1,3-dithianyl, and 1,4-dithianyl; examples of 7 membered heterocycloalkyl include, but are not limited to, azacycloheptanyl, oxacycloheptanyl and thiocycloheptanyl. Preferably, the heterocycloalkyl is a monocyclic heterocycloalkyl having 5 or 6 ring atoms.

[0072] The term "heterocyclohydrocarbyl" refers to a nonaromatic monocyclic, fused polycyclic, bridged cyclic or spiro cyclic group, wherein some ring atoms are heteroatoms selected from the group consisting of N, O, and S(O)_n (*n* is 0, 1 or 2), while the remaining ring atoms are C. Such a ring can be saturated or unsaturated (for example, with one or more double bonds), but does not have a fully conjugated π -electron system. Examples of 3 membered heterocyclohydrocarbyl include, but are not limited to, oxiranyl, thiiranyl and aziranyl; examples of 4 membered heterocyclohydrocarbyl include, but are not limited to, azetidiny, oxetanyl and thietanyl; examples of 5 membered heterocyclohydrocarbyl include, but are not limited to, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, isoxazolidinyl, oxazolidinyl, isothiazolidinyl, 1,1-dioxidoisothiazolidinyl, thiazolidinyl, imidazolidinyl, tetrahydropyrazolyl, pyrrolinyl, dihydrofuranyl and dihydrothienyl; ex-

amples of 6 membered heterocyclohydrocarbonyl include, but are not limited to, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, piperazinyl, 1,4-thioxanyl, 1,4-dioxanyl, thiomorpholinyl, 1,2- and 1,4-dithianyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyranyl, tetrahydropyranyl and dihydrothiopyranyl; examples of 7 membered heterocyclohydrocarbonyl include, but are not limited to, azacycloheptanyl, oxacycloheptanyl, thiocycloheptanyl, oxazabicyclo[2.2.1]heptyl, azaspiro[3.3]heptyl and the like.

[0073] The term "aryl" refers to an aromatic monocyclic or fused polycyclic group of carbon atoms with the conjugated π -electron system. For example, an aryl may have 6-20 carbon atoms, 6-14 carbon atoms or 6-12 carbon atoms. Non-limiting examples of aryl include, but are not limited to, phenyl, naphthyl, anthryl, 1,2,3,4-tetrahydronaphthalenyl, and the like.

[0074] The term "heteroaryl" refers to a monocyclic or fused polycyclic system containing at least one ring atom selected from the group consisting of N, O and S, with the remaining ring atoms being C, and having at least one aromatic ring. Preferably, heteroaryl has a single 5-8 membered ring, or a fused polycyclic system containing 6-14 ring atoms, in particular 6-10 ring atoms. Non-limiting examples of heteroaryl include, but are not limited to, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, tetrazolyl, triazolyl, triazinyl, benzofuranyl, benzothienyl, indolyl, isoindolyl and the like.

[0075] The compound disclosed herein can be asymmetrical, for example, has one or more stereoisomers. Unless otherwise stated, all stereoisomers are included, for example, enantiomers and diastereoisomers. The compound with asymmetric carbon atoms disclosed herein can be separated in an optically pure form or in a racemic form. The optically pure form can be separated from a racemic mixture or can be synthesized using a chiral raw material or a chiral reagent.

[0076] The terms "administer", "administration" and "administering" refer to physically introducing the composition comprising a therapeutic agent to an entity using any of various methods and delivery systems known to those skilled in the art.

[0077] The term "treating" and "treatment" usually refers to acquiring needed pharmacological effect and/or physiological effect. In terms of partially or fully stabilizing or curing the disease and/or a side effect of the disease, the effect can be therapeutic. As used herein, "treating" and "treatment" encompasses any treatment of a disease in a patient, including (a) inhibiting a symptom of the disease, i.e., blocking the progression of the disease; or (b) alleviating a symptom of the disease, i.e., causing remission of the disease or the symptom.

[0078] The term "effective amount" refers to an amount of the compound disclosed herein for (i) treating or preventing a specific disease, condition or disorder; (ii) alleviating, relieving or eliminating one or more symptoms of a specific disease, condition or disorder, or (iii) preventing or delaying onset of one or more symptoms of a specific disease, condition or disorder disclosed herein. The amount of the compound disclosed herein composing the "therapeutically effective amount" varies dependently on the compound, the disease state and its severity, the mode of administration, and the age of the mammal to be treated, but can be determined routinely by those skilled in the art in accordance with their knowledge and the present disclosure.

[0079] The term "subject" can be a mammal. In some embodiments, the subject is a mouse. In some embodiments, the subject is a human.

[0080] As used herein, the compound of formula I or the pharmaceutically acceptable salt thereof may be administered by any applicable routes and methods, for example, oral administration or parenteral (for example, intravenous) administration. The therapeutically effective amount of the compound of formula I or the pharmaceutically acceptable salt thereof includes, but is not limited to, from about 0.0001 to 20 mg/kg/d, for example, from 0.001 to 10 mg/kg/d. The dosing frequency (e.g., once, twice or more times daily) of the compound of formula I or the pharmaceutically acceptable salt thereof can be determined according to the requirements of the patient individuals, comprising the severity of the disease, the response of the disease, any treatment-related toxicity, and the age and health of the patient. Administration can be intermittent, for example, in a period of several days, the subject receives a daily dosage of the compound of formula I or the pharmaceutically acceptable salt thereof, and in the following period of the several days or more days, the patient does not receive the daily dosage of the compound of formula I or the pharmaceutically acceptable salt thereof.

[0081] Entecavir can be administered in various routes including, but not limited to, oral, parenteral, intraperitoneal, intravenous, intra-arterial, transdermal, sublingual, intramuscular, rectal, transbuccal, intranasal, inhalational, vaginal, intraocular, topical, subcutaneous, intralipid, intraarticular, intraperitoneal and intrathecal administrations. In some specific embodiments, the drug is administered orally. The amount of entecavir administered can be determined according to the severity of the disease, the response of the disease, any treatment-related toxicity, and the age and health of a patient. For example, a daily dose for administering entecavir can be 0.005 mg to 10.0 mg. Entecavir can be administered once or more times daily. In some embodiments, entecavir is administered once daily in an oral solid formulation.

[0082] The term "about" shall be understood to include within three standard deviations of the mean or within standard ranges of tolerance in the specific art. In some embodiments, the term "about" shall be understood as a variation not exceeding 0.5. The term "about" modifies all listed values thereafter. For example, "about 1, 2 and 3" represents "about 1", "about 2" and "about 3".

[0083] The term "pharmaceutical combination" refers to combined use of two or more active ingredients in a simulta-

neous, concurrent or sequential manner.

[0084] The term "fixed combination" refers to the active ingredients (such as TLR7 agonists or entecavir) are administered to a subject simultaneously in a fixed total dose or dose ratio, or in the form of a single entity, pharmaceutical composition or formulation. In some embodiments, for example, the active ingredients are in the same tablet or the same capsule or the same sachet.

[0085] The term "non-fixed combination" refers to two or more active ingredients as independent entities (such as pharmaceutical compositions, pharmaceutical preparations) administered to an individual simultaneously, concurrently or sequentially without any specific time limit, wherein the active ingredients administered to the individual reach therapeutically effective amounts. An example, which can be enumerated, of the non-fixed combination is a cocktail therapy, for example, 2, 3 or more active ingredients are administered. In a non-fixed combination, each active ingredient can be packaged, sold or administered as a fully independent pharmaceutical composition. The "non-fixed combination" further includes combined use of "fixed combinations" the "fixed combination" with any one or more independent entities of active ingredients.

[0086] The term "pharmaceutical composition" refers to a mixture comprised of one or more of the compounds or the pharmaceutically acceptable salts thereof, or the pharmaceutical combinations thereof disclosed herein and a pharmaceutically acceptable excipient. The pharmaceutical composition is intended to facilitate the administration of the compound or the pharmaceutical combination thereof disclosed herein to a subject.

[0087] The term "pharmaceutically acceptable" is used herein for those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications, and commensurate with a reasonable benefit/risk ratio.

[0088] The term "pharmaceutically acceptable salt" refers to salts of the compounds disclosed herein that are within the definition of "pharmaceutically acceptable".

[0089] Unless otherwise specified, terms in the singular shall be deemed to include the plural and vice versa. Unless otherwise specified, the word "a" or "an" refers to "at least one". Unless otherwise stated, use of "or" means "and/or".

[0090] As used herein, the terms "comprise", "comprises" and "comprising" or equivalents thereof are open-ended statements and mean that elements, components and steps that are not specified may be included in addition to those listed, unless otherwise stated.

[0091] All patents, patent applications and other identified publications are expressly incorporated herein by reference for the purpose of description and disclosure. These publications are provided solely because they were disclosed prior to the filing date of the present application. All statements as to the dates of these documents or description as to the contents of these documents are based on the information available to the applicant and do not constitute any admission as to the correctness of the dates or the content of these documents. Moreover, in any country or region, any reference to these publications herein is not to be construed as an admission that the publications form part of the commonly recognized knowledge in the art.

Administration

[0092] The content below is not intended to limit the administration of the pharmaceutical combination disclosed herein. The active ingredients in the pharmaceutical combination disclosed herein can be formulated separately, or some or all of the active ingredients are co-formulated. In one embodiment, the pharmaceutical combination disclosed herein can be formulated into a pharmaceutical composition which is suitable for a single dose or multiple doses. The active ingredients in the pharmaceutical combination disclosed herein can be administered separately, or some or all of the active ingredients are co-administered. The ingredients of the pharmaceutical combination disclosed herein can be administered in a substantially asynchronous manner, or some or all of the ingredients are administered in a substantially synchronous manner.

[0093] The active ingredients in the pharmaceutical combination disclosed herein can be administered independently, or some or all of the active ingredients are co-administered in various proper routes, including, but not limited to, oral administration or parenteral administration (intravenous, intramuscular, local or subcutaneous routes). In some embodiments, the active ingredients in the pharmaceutical combination disclosed herein can be administered independently, or some or all of the active ingredients are co-administered by means of oral administration or injection, for example, intravenous injection or intraperitoneal injection.

[0094] The active ingredients in the pharmaceutical combination disclosed herein can be in independent suitable dosage forms, or some or all of the active ingredients are co-formulated in a suitable dosage form, including, but not limited to, tablet, lozenge, pill, capsule (for example, hard capsule, soft capsule, enteric capsule and microcapsule), elixir, granule, syrup, injection (intramuscular, intravenous and intraperitoneal), powder, emulsion, suspension, solution, dispersion and dosage forms of sustained-release preparations for oral or non-oral administration.

[0095] The active ingredients in the pharmaceutical combination disclosed herein can be each independently formu-

lated with a pharmaceutically acceptable carrier and/or excipient, or some or all of the active ingredients are co-formulated with a pharmaceutically acceptable carrier and/or excipient.

[0096] The pharmaceutical combination disclosed herein may further comprise an additional therapeutic agent. In one embodiment, the additional therapeutic agent can be a therapeutic agent known in the art for treating hepatitis B virus infection.

[0097] In some embodiments, the effective amounts of the compound of formula I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof disclosed herein can be administered to a subject in need thereof simultaneously, sequentially or at intervals.

[0098] In some embodiments, the effective amounts of the compound of formula I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof can be administered to a subject in need thereof in the same regimen or in different regimens.

[0099] In some embodiments, the compound of formula I or the pharmaceutically acceptable salt thereof is administered thrice every day, twice every day, once every day, once every two days, once every three days, once every four days, once every five days, once every six days, once every week, once every two weeks or once every three weeks.

[0100] In some embodiments, the compound of formula I or the pharmaceutically acceptable salt thereof is administered at a dose of 0.1 to 10.0 mg each time, preferably a dose of 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2.0 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6 mg, 2.7 mg, 2.8 mg, 2.9 mg, 3.0 mg, 3.1 mg, 3.2 mg, 3.3 mg, 3.4 mg, 3.5 mg, 3.6 mg, 3.7 mg, 3.8 mg, 3.9 mg, 4.0 mg, 4.1 mg, 4.2 mg, 4.3 mg, 4.4 mg, 4.5 mg, 4.6 mg, 4.7 mg, 4.8 mg, 4.9 mg, 5.0 mg, 5.1 mg, 5.2 mg, 5.3 mg, 5.4 mg, 5.5 mg, 5.6 mg, 5.7 mg, 5.8 mg, 5.9 mg, 6.0 mg, 6.1 mg, 6.2 mg, 6.3 mg, 6.4 mg, 6.5 mg, 6.6 mg, 6.7 mg, 6.8 mg, 6.9 mg, 7.0 mg, 7.1 mg, 7.2 mg, 7.3 mg, 7.4 mg, 7.5 mg, 7.6 mg, 7.7 mg, 7.8 mg, 7.9 mg, 8.0 mg, 8.1 mg, 8.2 mg, 8.3 mg, 8.4 mg, 8.5 mg, 8.6 mg, 8.7 mg, 8.8 mg, 8.9 mg, 9.0 mg, 9.1 mg, 9.2 mg, 9.3 mg, 9.4 mg, 9.5 mg, 9.6 mg, 9.7 mg, 9.8 mg, 9.9 mg, 10.0 mg, or a range formed by any of the values. In some embodiments, the compound of formula I or the pharmaceutically acceptable salt thereof is administered at a dose of 0.2 to 5.0 mg, 0.4 to 4.0 mg, 0.5 to 3.0 mg, 0.6 to 2.6 mg, 0.8 to 2.2 mg, 0.8 to 1.8 mg, 1.0 to 2.0 mg, 1.0 to 1.8 mg or 1.0 to 1.6 mg each time.

[0101] In some embodiments, the compound of formula I or the pharmaceutically acceptable salt thereof is administered once every week at a dose of 0.2 to 5.0 mg, 0.4 to 4.0 mg, 0.5 to 3.0 mg, 0.6 to 2.6 mg, 0.8 to 2.2 mg, 0.8 to 1.8 mg, 1.0 to 2.0 mg, 1.0 to 1.8 mg or 1.0 to 1.6 mg each time. In some embodiments, the compound of formula I or the pharmaceutically acceptable salt thereof is administered once every week at a dose of 1.0 to 1.8 mg each time. In some embodiments, entecavir or the pharmaceutically acceptable salt or solvate thereof is administered thrice every day, twice every day, once every day, once every two days, once every three days, once every four days, once every five days, once every six days, once every week, once every two weeks or once every three weeks.

[0102] In some embodiments, entecavir or the pharmaceutically acceptable salt or solvate thereof is administered at a dose of 0.005 mg to 5.0 mg each time, preferably a dose of 0.01 mg, 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2.0 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6 mg, 2.7 mg, 2.8 mg, 2.9 mg, 3.0 mg, 3.1 mg, 3.2 mg, 3.3 mg, 3.4 mg, 3.5 mg, 3.6 mg, 3.7 mg, 3.8 mg, 3.9 mg, 4.0 mg, 4.1 mg, 4.2 mg, 4.3 mg, 4.4 mg, 4.5 mg, 4.6 mg, 4.7 mg, 4.8 mg, 4.9 mg, 5.0 mg, or a range formed by any of the values. In some embodiments, entecavir or the pharmaceutically acceptable salt or solvate thereof is administered at a dose of 0.05 mg to 5.0 mg, 0.10 mg to 2.0 mg, 0.25 mg to 2.0 mg or 0.5 mg to 1.0 mg each time.

[0103] In some embodiments, entecavir or the pharmaceutically acceptable salt or solvate thereof is administered once daily at a dose of 0.10 mg to 2.0 mg each time. In some embodiments, entecavir or the pharmaceutically acceptable salt or solvate thereof can be administered once daily at a dose of 0.5 mg each time.

[0104] In some embodiments, the TLR7 agonist (i.e., the compound of formula I) is administered once every week at a dose of 1.0 to 1.8 mg each time; entecavir is administered once every day at a dose of 0.5 mg each time.

Technical Effects

[0105] The pharmaceutical composition can significantly reduce the HBV DNA level or relieve other HBV markers. In addition, the pharmaceutical combination disclosed herein demonstrates a significant enhancement compared to monotherapies. These indicate that the pharmaceutical combination disclosed herein has good pharmaceutical value.

DRAWING OF THE SPECIFICATION

[0106] Figure 1 illustrates effect of a TLR7 agonist on serum HBV DNA replication levels in AAV mice.

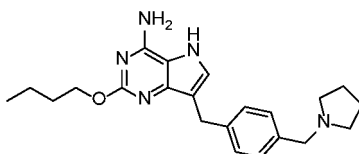
DETAILED DESCRIPTION

[0107] For the sake of clarity, the present application is further illustrated by examples, which are, however, not intended to limit the scope of the present application. All reagents are commercially available and can be used without further purification.

Example 1. AAV Mice Study

1.1. Test compounds

[0108] In this example, the TLR7 agonist was



(2-butoxy-7-(4-(pyrrolidin-1-ylmethyl) benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine); see WO2016023511 for the preparation method.

[0109] In this example, the entecavir used is a monohydrate thereof.

1.2. Method and grouping

[0110] Male C57BL/6 mice (Shanghai Slac Laboratory Animal Co., Ltd.) aged 6-8 weeks were taken, and rAAV8-1.3HBV virus (FivePlus Institute of Molecular Medicine, Beijing) was injected into the C57BL/6 mice via tail veins at a dose of 1×10^{11} vg. Blood was collected from the orbit at week 2 and week 4 after the virus was injected. Serum was separated, and HBV DNA copy number in serum were measured to determine whether the model was successfully constructed or not. Mice were randomized according to the HBV DNA copy number into vehicle control group, TLR7 agonist group (20 mg/kg, tiw), entecavir (ETV) group (0.0032 (week 1, 1 W) & 0.001 (week 2-6, 2-6 W) mg/kg, qd), and TLR7 agonist and ETV combination group, each group containing 6 mice. The mice in each group were administered intragastrically for 6 weeks, and the administration was stopped for 3 week. Blood was collected from the orbit at weeks 1, 2, 3, 4, 5 and 6 during the administration period and weeks 1, 2 and 3 during the withdrawal period, and serum was separated. The HBV DNA copy number was determined by fluorescence quantitative PCR.

[0111] Groups:

- i. Vehicle control group;
- ii. Monotherapy group: entecavir;
- iii. Monotherapy group: TLR7 agonist;
- iv. Combination group (combo): TLR7 agonist and entecavir;

Table 1-1. Dosing regimen

Group	Dosage (mg/kg)	Administration Route	Administration interval	Administration cycle
i.	----	i.g.	qd	6w
ii.	0.0032 (1W) & 0.001 (2-6W)	i.g.	qd	6w
iii.	20 (TLR7 agonist)	i.g.	tiw	6w
iv.	20 (TLR7 agonist)	i.g.	tiw	6w
	0.0032 (1 W) & 0.001 (2-6 W) (entecavir)	i.g.	qd	6w

Note: i.g.: intragastric; qd: once daily; tiw: once every three days; 6 w: six weeks. The administration of the combination group was consistent with that of the monotherapy groups.

1.3. Method for evaluating pharmaceutical combination

[0112] The test results were evaluated by Jin equation. The Jin equation is a modified method based on the Burgi method, and is also referred to the probability addition method:

The combination efficacy is calculated according to the following equation: $q = E_{A+B}/(E_A + E_B - E_A \times E_B)$ wherein E_A denotes the efficacy of drug A monotherapy; E_B denotes the efficacy of drug B monotherapy; E_{A+B} denotes the efficacy of the combination of drugs A and B.

[0113] The significance of q: 0.85 to 1.15 indicates simple addition; 1.15 to 20 indicates enhancement; greater than 20 indicates significant enhancement; 0.85 to 0.55 indicates antagonism; less than 0.55 indicates significant antagonism. The q value takes the absolute value.

1.4. Results

[0114] The results are shown in Table 1-2, Table 1-3, Table 1-4 and FIG. 1.

Table 1-2. Efficacy of different therapies on HBV DNA replication level ($\log_{10}$ IU/mL) in mouse serum (treatment period)

Group	Treatment period (d)						
	0	7	14	21	28	35	42
i.	7.57±0.17	7.31±0.23	7.31±0.31	6.79±0.47	6.72±0.53	6.95±0.58	7.23±0.67
ii.	7.53±0.15	5.27±0.18 ***	5.66±0.14 ***	5.96±0.28 ***	5.34±0.43 ***	5.62±0.36 ***	6.44±0.46*
iii.	7.53±0.15	6.64±1.33	4.55±1.41 ***	4.13±0.67 ***	3.64±0.21 ***	3.61±0.24 ***	3.41±0.33***
iv.	7.50±0.13	4.15±0.76 ***	2.48±0.81 ***	***2.62± 0.74 ***	1.82±0.54 ***	2.32±0.16 ***	2.42±0.31***

Note: comparison with the vehicle control group, where *P < 0.05, **P < 0.01, ***P < 0.001.

Table 1-3. Efficacy of different therapies on HBV DNA replication level ($\log_{10}$ IU/mL) in mouse serum (withdrawal period)

Group	Withdrawal period (d)		
	49	56	63
i.	7.40±0.49	7.51±0.48	7.54±0.34
ii.	6.97±0.72	7.32±0.73	7.33±0.80
iii.	4.37±0.48***	4.86±0.41***	5.26±0.39***
iv.	3.60±0.32***	3.96±0.55***	5.71±0.68***

Note: comparison with the vehicle control group, where *P < 0.05, **P < 0.01, ***P < 0.001.

Table 1-4. Evaluation of combination therapy by Jin equation

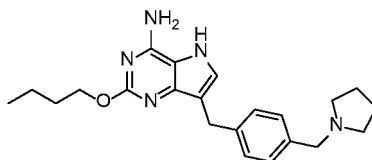
	Treatment period (d)					
	7	14	21	28	35	42
q value	2.35	33.54	3.25	23.38	20.32	3.02

[0115] Over a 42-day treatment period, HBV DNA was significantly reduced in the monotherapy groups of entecavir and TLR7 agonist (groups ii and iii); the combination group (group iv) also demonstrated significantly reduced HBV DNA, and q-value results indicated that the combination therapy exhibited superior synergic effect.

Example 2

1. Test compounds

[0116] In this example, the TLR7 agonist was



(2-butoxy-7-(4-(pyrrolidin-1-ylmethyl) benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine); see WO2016023511 for the preparation method. The compound was prepared into tablets with strength of 0.2 mg or 0.5 mg.

[0117] Entecavir: commercially available entecavir tablets with strength of 0.5 mg. Commercially available entecavir tablets include, but are not limited to, entecavir dispersible tablets (Runzhong®).

[0118] Placebo: a placebo for TLR7 agonist.

2. Enrolled subjects

[0119] The subject should meet all of the following criteria:

1) Male patients or non-pregnant, non-lactating female patients aged 18-65 years (inclusive);

2) Serum virology: persistent positive serum HBsAg for 6 months or more, or with evidence of chronic hepatitis B for 6 months;

3) Previously treated patients: historical HBV DNA inhibition less than the lower limit of normal 24 weeks before enrollment, and HBV DNA inhibition defined as <69 IU/mL determined by a Roche reagent during screening; Fibroscan $\leq$ 9.0 Kpa (fasting), and ALT $\leq$ 5 $\times$ ULN;

4) Previously untreated patients: HBV DNA > 10⁵ copies/mL (or > 20000 IU/mL) for HBeAg-positive chronic hepatitis B patients or HBV DNA > 10⁴ copies/mL (or > 2000 IU/mL) for HBeAg-negative patients as determined by Roche's Cobas Taqman real-time quantitative PCR test v2.0, with the lower limit of detection being 20 IU/mL; Fibroscan $\leq$ 12.4 Kpa (fasting), and 1 $\times$ ULN $\leq$ ALT $\leq$ 5 $\times$ ULN. The previously untreated patients mean that the patients did not receive antiviral therapies against HBV or participate in related clinical trials.

3. Dosage and administration

[0120] TLR7 agonist: once weekly.

[0121] Entecavir: 0.5 mg/day, once daily.

[0122] The first group included 12 subjects, of which 8 received 1.2 mg of the TLR7 agonist in combination with entecavir and 4 received placebo in combination with entecavir for 24 weeks.

[0123] The second, third and fourth groups each included 36 subjects randomly subgrouped in a ratio of TLR7 agonist : placebo = 5:1. The three groups respectively received 1.0 mg of TLR7 agonist combined with entecavir or placebo combined with entecavir (the second group), 1.5 mg of TLR7 agonist combined with entecavir or placebo combined with entecavir (the third group), and 1.8 mg of TLR7 agonist combined with entecavir or placebo combined with entecavir (the fourth group). The groups were treated for 24 weeks.

4. Efficacy endpoints

[0124] Efficacy endpoints: serum HBsAg, HBeAg, or HBV DNA, etc.

[0125] Exploratory endpoints: HBV RNA and HBcrAg, etc.

[0126] The mean, standard deviation, median, quartile, minimum and maximum values were used to describe the average content of the index parameters at each detection time point in each group and the change from baseline; the mixed-effects model for repeated measures (MMRM) was used, with group, baseline, detection time point, and the interaction term of group and detection time point as fixed effects and the subject and the intercept term as random

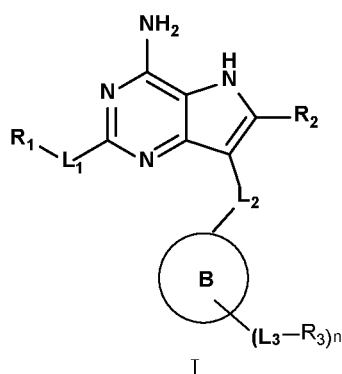
effects, the changes from baseline of the index parameters at each detection time point in treatment group were compared with those of the placebo groups, respectively, and corrected by the Dunnett's test.

5. Results

[0127] All of the TLR7 agonist and entecavir combination groups showed significantly inhibition on HBV DNA replication. All of the TLR7 agonist and placebo combinations achieved inhibition of HBV DNA replication. The entecavir and placebo combinations also had inhibitory effects on HBV DNA replication.

Claims

1. A pharmaceutical combination, comprising a compound of formula I or a pharmaceutically acceptable salt thereof and entecavir or a pharmaceutically acceptable salt or solvate thereof, the compound of formula I is shown as follows:



wherein,

L_1 is selected from -O-;

L_2 is selected from -CH₂-, wherein the -CH₂- is optionally substituted with R_4 ;

R_1 is selected from the group consisting of hydrogen and C₁₋₁₀ alkyl, wherein the C₁₋₁₀ alkyl is optionally substituted with R_5 ;

R_2 is selected from the group consisting of hydrogen, cyano, -COOH and -CONH₂, wherein the -COOH and -CONH₂ are optionally substituted with R_6 ;

B is selected from the group consisting of 6-10 membered aryl and 5-10 membered heteroaryl;

L_3 is selected from the group consisting of C₀₋₆ alkylene and imino, wherein the C₀₋₆ alkylene and imino are optionally substituted with R_7 ;

R_3 is selected from the group consisting of hydrogen, amino, C₁₋₁₀ alkyl, C₃₋₁₀ cyclohydrocarbyl, 3-10 membered heterocyclohydrocarbyl, 6-10 membered aryl and 5-10 membered heteroaryl, wherein the amino, C₁₋₁₀ alkyl, C₃₋₁₀ cyclohydrocarbyl, 3-10 membered heterocyclohydrocarbyl, 6-10 membered aryl and 5-10 membered heteroaryl are optionally substituted with R_8 , or

R_3 and L_3 , together with an ortho atom on ring B, form a saturated or unsaturated 5-8 membered ring, wherein the 5-8 membered ring is optionally substituted with R_9 ;

n is 0, 1, 2, 3, 4 or 5;

R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are each independently selected from halogen, cyano, hydroxy, sulfydryl, amino, -R, -OR, =O, -SR, -NHR and -NR₂; R is independently selected from the group consisting of C₁₋₈ alkyl, C₃₋₈ cyclohydrocarbyl, 3-8 membered heterocyclohydrocarbyl, 6-8 membered aryl and 5-8 membered heteroaryl.

2. The pharmaceutical combination according to claim 1, wherein the compound of formula I or the pharmaceutically acceptable salt thereof is selected from the group consisting of:

2-butoxy-7-(3-((4-methylpiperazin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

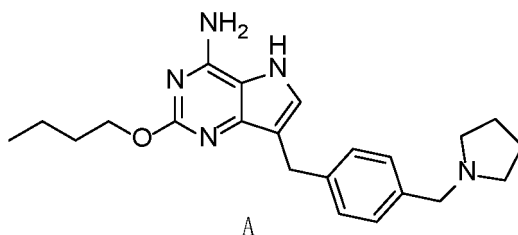
2-butoxy-7-(3-(morpholinomethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

7-(3-(aminomethyl)benzyl)-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(3-(pyrrolidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;

2-butoxy-7-(4-((3,3-difluoropyrrolidin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-((3-fluoropyrrolidin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 1-(4-((4-amino-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)benzyl)pyrrolidin-3-ol;
 2-butoxy-7-(4-(piperidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-(morpholinomethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-((4-methylpiperazin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-((dimethylamino)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-((diethylamino)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-((dipropylamino)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 7-(4-(azetidin-1-ylmethyl)benzyl)-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-((3-methoxylazetidin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-(4-methyl-1,4-diazepan-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-((2,6-dimethylmorpholino)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 7-(4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-ylmethyl)benzyl)-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-((4-methoxypiperidin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-((4-isopropylpiperazin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-((6-(pyrrolidin-1-ylmethyl)pyridin-3-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(3-(2-(pyrrolidin-1-yl)ethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-(1-(pyrrolidin-1-yl)ethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-(1-methylpiperidin-4-yl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-(4-(1-methylpyrrolidin-2-yl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 1-(4-((4-amino-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)phenyl)-4-methylpiperazin-2-one;
 7-benzyl-2-(2-methoxyethoxy)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-(2-methoxyethoxy)-7-((6-methylpyridin-3-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 7-((5-chloropyridin-2-yl)methyl)-2-(2-methoxyethoxy)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-(2-methoxyethoxy)-7-((6-(pyrrolidin-1-ylmethyl)pyridin-3-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 1-(4-((4-amino-2-(2-methoxyethoxy)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)methyl)phenyl)-4-methylpiperazin-2-one;
 2-butoxy-7-((5-(pyrrolidin-1-ylmethyl)pyridin-2-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 4-amino-2-butoxy-7-((6-(pyrrolidin-1-ylmethyl)pyridin-3-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-6-carbonitrile;
 4-amino-2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-6-carbonitrile;
 4-amino-2-butoxy-7-(4-(morpholinomethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-6-carbonitrile;
 4-amino-2-butoxy-7-(4-((4-methylpiperazin-1-yl)methyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-6-carbonitrile;
 4-amino-2-butoxy-7-(4-(pyrrolidin-1-ylmethyl)benzyl)-5H-pyrrolo[3,2-d]pyrimidin-6-carboxamide;
 2-butoxy-7-((1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-((2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-((2-ethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-((2-isopropyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-((1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine;
 2-butoxy-7-((2-ethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine; and
 2-butoxy-7-((2-(pyrrolidin-1-ylmethyl)thiazol-5-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine, or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical combination according to claim 1 or 2, wherein the compound of formula I in the pharmaceutical combination is selected from a compound of formula A



4. The pharmaceutical combination according to claim 1, wherein entecavir or the pharmaceutically acceptable salt or solvate thereof is selected from entecavir maleate, entecavir monomaleate, entecavir hydrate, entecavir 0.5-2 hydrate, and entecavir monohydrate; optionally, entecavir or the pharmaceutically acceptable salt or solvate thereof is selected from entecavir monomaleate monohydrate.
5. The pharmaceutical combination according to any of claims 1 to 4, wherein an average daily dose ratio of the compound of formula I or the pharmaceutically acceptable salt thereof to entecavir or the pharmaceutically acceptable salt or solvate thereof in the pharmaceutical combination is selected from 10:1 to 1:10; optionally, the average daily dose ratio is selected from the group consisting of 1:1.5 to 1:4, 1:1.6 to 1:3.8, 1:1.8 to 1:3.8, 1:1.8 to 1:3.6 and 1:2 to 1:3.5.
6. The pharmaceutical combination according to any of claims 1 to 5, wherein the compound of formula I or the pharmaceutically acceptable salt thereof in the pharmaceutical combination is administered thrice every day, twice every day, once every day, once every two days, once every three days, once every four days, once every five days, once every six days, once every week, once every two weeks or once every three weeks.
7. The pharmaceutical combination according to any of claims 1 to 6, wherein the compound of formula I or the pharmaceutically acceptable salt thereof in the pharmaceutical combination is administered at a dose of 0.1 to 10.0 mg each time; optionally, the compound of formula I or the pharmaceutically acceptable salt thereof is administered at a dose of 0.2 to 5.0 mg, 0.4 to 4.0 mg, 0.5 to 3.0 mg, 0.6 to 2.6 mg, 0.8 to 2.2 mg, 0.8 to 1.8 mg, 1.0 to 2.0 mg, 1.0 to 1.8 mg, or 1.0 to 1.6 mg each time.
8. The pharmaceutical combination according to any of claims 1 to 7, wherein entecavir or the pharmaceutically acceptable salt or solvate thereof in the pharmaceutical combination is administered thrice every day, twice every day, once every day, once every two days, once every three days, once every four days, once every five days, once every six days, once every week, once every two weeks or once every three weeks.
9. The pharmaceutical combination according to any of claims 1 to 8, wherein entecavir or the pharmaceutically acceptable salt or solvate thereof in the pharmaceutical combination is administered at a dose of 0.005 mg to 5.0 mg each time; optionally, entecavir or the pharmaceutically acceptable salt or solvate thereof is administered at a dose of 0.05 mg to 5.0 mg, 0.10 mg to 2.0 mg, 0.25 mg to 2.0 mg, or 0.5 mg to 1.0 mg each time.
10. The pharmaceutical combination according to any of claims 1 to 9, wherein the pharmaceutical combination is a fixed combination; optionally, the fixed combination is in the form of a solid pharmaceutical composition; optionally, the compound of formula I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof in the fixed combination are present in the same solid pharmaceutical composition.
11. The pharmaceutical combination according to any of claims 1 to 9, wherein the pharmaceutical combination is a non-fixed combination; optionally, the compound of formula I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof in the non-fixed combination are each in the form of a solid pharmaceutical composition; optionally, the compound of formula I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof in the non-fixed combination are each in the form of a solid pharmaceutical composition, and the solid pharmaceutical composition of the compound of formula I or the pharmaceutically acceptable salt thereof and the solid pharmaceutical composition of entecavir or the pharmaceutically acceptable salt or solvate thereof are present in the same sachet; optionally, the compound of formula I or the pharmaceutically acceptable salt thereof and entecavir or the pharmaceutically acceptable salt or solvate thereof in the non-fixed combination are each in the form of a solid pharmaceutical composition, and the solid pharmaceutical composition of the compound of formula I or the pharmaceutically acceptable salt thereof and the solid pharmaceutical composition of entecavir or the pharmaceutically acceptable salt or solvate thereof are not present in the same sachet.
12. Use of the pharmaceutical combination according to any of claims 1 to 11 for the manufacture of a medicament for treating hepatitis B virus infection.
13. A method of treating hepatitis B virus infection, comprising administering to a subject in need thereof an effective amount of the pharmaceutical combination according to any of claims 1 to 11.
14. A pharmaceutical combination for use in treating hepatitis B virus infection, wherein the pharmaceutical combination

is selected from the pharmaceutical combination according to any of claims 1 to 11.

15. Use of the pharmaceutical combination according to any of claims 1 to 11 in treating hepatitis B virus infection.

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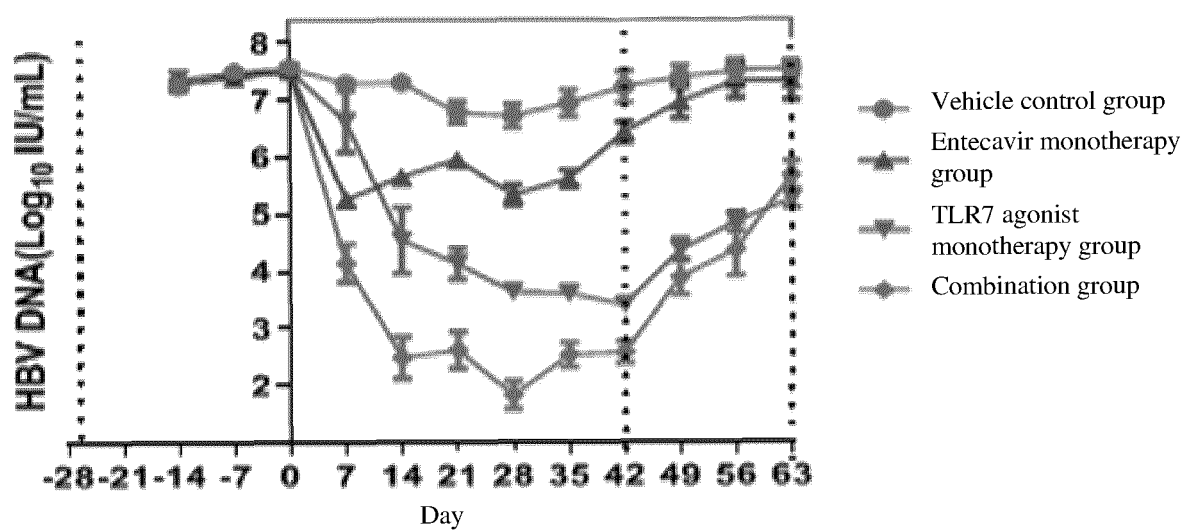


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2020/118693

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/519(2006.01)i; A61K 31/522(2006.01)i; A61P 31/20(2006.01)i; A61P 31/12(2006.01)i; C07D 471/04(2006.01)i; C07D 487/04(2006.01)i; C07D 207/02(2006.01)i; C07D 265/28(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K,C07D,A61P,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS, CNTXT, DWPI, SIPOABS, USTXT, EPTXT, WOTXT, CNKI, GOOGLE, STN, 正大天晴, 强生, 古里德科学, 乙肝, 乙型肝炎, 恩替卡韦, 核苷类似物, TLR, 激动剂, 联用, 协同, Janssen, Gilead Sci INC, hepatitis B, HBV, entecavir, nucleoside analogues, TLR-7, toll like receptor, agonist, combin+, synerg+, TQ-A3334, AL-034, JNJ-4964, GS-9620, 1228585-88-3, 1878111-20-6

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 2020188448 A1 (JOHJ JANSSEN SCI IRELAND UNLIMITED CO.) 24 September 2020 (2020-09-24) description, page 12, line 16 to page 18, line 1, page 44, line 15 to page 46, line 18 and page 59, lines 33-35	1-15
PX	CHIA TAI TIANQING PHARMACEUTICAL GROUP CO. LTD., "A study of TQ-A3334 Combined with entecavir in the Treatment of Chronic Hepatitis B;" https://clinicaltrials.gov/ct2/show/NCT04180150 , 16 December 2019 (2019-12-16), study description section	1-15
Y	ANTONIO Goncalves et al. "Modeling HBV kinetics in mice treated by a novel TLR7 agonist, alone or in combination with entecavir;" <i>Journal of Hepatology</i> , Vol. 70, No. 1, 01 April 2019 (2019-04-01), page e465 right-hand column lines 4-48	1-15
Y	CN 105367576 A (CHIA TAI TIANQING PHARMACEUTICAL GROUP CO., LTD.) 02 March 2016 (2016-03-02) description, paragraphs [0001], [0003]-[0032], [0040], [0041]	1-15

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

17 December 2020

Date of mailing of the international search report

04 January 2021

Name and mailing address of the ISA/CN

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Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2020/118693

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KOROLOWICZ Kyle E et al. "Liver-Targeted Toll-Like Receptor 7 Agonist Combined With Entecavir Promotes a Functional Cure in Woodchuck Model of Hepatitis B Virus;" <i>Hepatology Communications</i> , Vol. 3, No. 10, 08 July 2019 (2019-07-08), study description section	1-15
Y	CN 102272134 A (GILEAD SCIENCES, INC.) 07 December 2011 (2011-12-07) claims 29-31, description paragraph [0001]	1-15

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2020/118693

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **13, 15**
because they relate to subject matter not required to be searched by this Authority, namely:
[1] Claim 13 relates to a method for treating hepatitis B infection, claim 15 relates to a use of the drug composition in any one of claims 1-11 in treating hepatitis B infection. The two claims thus belong to treatment methods for diseases, and do not comply with PCT Rule 39.1(iv). The present search report is provided on the basis of the subject matter names of claims 13 and 15 being amended as follows:
“a use of the drug composition in any one of claims 1-11 in preparing a drug for treating hepatitis B infection”.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2020/118693

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2020188448 A1	24 September 2020	None	
CN 105367576 A	02 March 2016	None	
CN 102272134 A	07 December 2011	IL 213101 A	31 December 2014
		TW 201639852 A	16 November 2016
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		US 8629142 B2	14 January 2014
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		PT 2364314 E	09 June 2014

Form PCT/ISA/210 (patent family annex) (January 2015)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/CN2020/118693

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
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		US 9127006 B2	08 September 2015

Form PCT/ISA/210 (patent family annex) (January 2015)

REFERENCES CITED IN THE DESCRIPTION

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